Type 1 versus type 3 neovascularization in pigment epithelial detachments associated with age-related macular degeneration after anti-vascular endothelial growth factor therapy: a prospective study

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Abstract: PURPOSE To evaluate the response to aflibercept therapy for Type 1 and Type 3 neovascularization in pigment epithelial detachments associated with treatment-naive, neovascular age-related macular degeneration. METHODS In this multicentered, prospective study, eligible eyes underwent an intravitreal aflibercept injection protocol for 12 months. Visual acuity and morphologic features of the pigment epithelial detachments were compared at baseline and follow-up intervals between eyes with Type 1 versus Type 3 neovascularization. RESULTS Thirty-six eyes were analyzed. At 12 months, Type 1 lesions showed a 4.5 ± 23 Early Treatment of Diabetic Retinopathy Study letter improvement (P = 0.1665) versus a 14 ± 11 (P = 0.0072) letter improvement with Type 3 lesions. Both Type 1 and 3 eyes showed a significant decrease in pigment epithelial detachment size, subretinal fluid, and subretinal hyperreflective material; however, Type 3 eyes had a greater reduction in pigment epithelial detachment size and subretinal hyperreflective material, as well as a reduction in central retinal thickness. Type 1 eyes required an average of 1.636 (range, 1-4) injections to resolve fluid, which was greater than Type 3 eyes, which required an average of 1.143 (range, 1-2) injections (P = 0.0251). CONCLUSION Intravitreal aflibercept injections were efficacious for pigment epithelial detachments, but baseline and follow-up anatomical and functional outcomes differed in Type 1 versus Type 3 neovascularization. The better response of Type 3 eyes with fewer injections suggests that differentiation of the neovascularization subtype at the initial diagnosis may allow for a more tailored, optimal therapy.

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TYPE 1 VERSUS TYPE 3 NEOVASCULARIZATION IN PIGMENT EPITHELIAL DETACHMENTS ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

A Prospective Study

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Purpose: To evaluate the response to aflibercept therapy for Type 1 and Type 3 neovascularization in pigment epithelial detachments associated with treatment-naive, neovascular age-related macular degeneration.

Methods: In this multicentered, prospective study, eligible eyes underwent an intravitreal aflibercept injection protocol for 12 months. Visual acuity and morphologic features of the pigment epithelial detachments were compared at baseline and follow-up intervals between eyes with Type 1 versus Type 3 neovascularization.

Results: Thirty-six eyes were analyzed. At 12 months, Type 1 lesions showed a 4.5 ± 23 Early Treatment of Diabetic Retinopathy Study letter improvement (P = 0.1665) versus a 14 ± 11 (P = 0.0072) letter improvement with Type 3 lesions. Both Type 1 and 3 eyes showed a significant decrease in pigment epithelial detachment size, subretinal fluid, and subretinal hyperreflective material; however, Type 3 eyes had a greater reduction in pigment epithelial detachment size and subretinal hyperreflective material, as well as a reduction in central retinal thickness. Type 1 eyes required an average of 1.636 (range, 1–4) injections to resolve fluid, which was greater than Type 3 eyes, which required an average of 1.143 (range, 1–2) injections (P = 0.0251).

Conclusion: Intravitreal aflibercept injections were efficacious for pigment epithelial detachments, but baseline and follow-up anatomical and functional outcomes differed in Type 1 versus Type 3 neovascularization. The better response of Type 3 eyes with fewer injections suggests that differentiation of the neovascularization subtype at the initial diagnosis may allow for a more tailored, optimal therapy.

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Serous and fibrovascular pigment epithelial detachments (PEDs) have been estimated to be present in 63% of eyes with neovascular age-related macular degeneration (AMD)[1] and are predominantly the result of either Type 1 or Type 3 neovascularization (NV). Type 1 NV originates from the choroid and is located underneath the retinal pigment epithelium (RPE), whereas Type 3 NV, also known as retinal angiomatous proliferation, generally originates from the deep retinal capillary plexus (DCP) within the retina.[2] Type 1 and Type 3 membranes comprise nearly 90% of lesions in neovascular AMD.[3]

Pigment epithelial detachments in neovascular AMD can be challenging to treat and may be more resistant to anti-vascular endothelial growth factor (anti-VEGF)

therapy with worse visual outcomes.[4,5] Although all subgroups of neovascular AMD have shown visual and anatomical benefits with any of the 3 major intravitreal anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept), certain studies have indicated that the visual outcomes may not be as favorable in eyes with PEDs.[4,5] None of these studies, however, have differentiated treatment response based on the subtype of NV. In fact, to date, there has been no prospective study comparing the effects of intravitreal aflibercept injections on treatment-naive PEDs due to Type 1 versus Type 3 NV in AMD.

The aim of this subanalysis study was to compare the clinical and multimodal imaging features of eyes with PEDs due to Type 1 versus Type 3 NV at baseline and to assess their comparative visual and anatomical response to intravitreal aflibercept injections in a prospective investigation. Visual and anatomical outcomes of the PED cohort as a whole will be published in a separate study.

Methods

Study Design

This multicentered trial was a prospective, noncontrolled, open-labeled, interventional, comparative clinical investigation. Institutional review board approval was obtained before the beginning of the study. The research trial adhered to the tenets of the Declaration of Helsinki and was conducted in accord with regulations set forth by the Health Insurance Portability and Accountability Act. All participants signed a written informed consent.

Patients at least 50 years of age with treatment-naive, active, neovascular AMD, submacular PED less than 12 disk areas with foveal involvement, and evidence of intraretinal fluid (IRF) and/or subretinal fluid (SRF) were enrolled for prospective assessment of visual outcomes from baseline to 12 months and prospective evaluation of lesion findings using multimodal imaging analysis. Vision criteria for recruitment included Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 19 and 73 letters (Snellen 20/35–20/400) in the affected eye. Pigment epithelial detachments were defined by multimodal retinal imaging with the following characteristics. A well-circumscribed, orange or yellow, oval or bean-shaped elevation of the RPE with a smooth, convex surface with or without a notch. Fluorescein angiography (FA) criteria included areas of uniform or leakage with or without a hot spot. Spectral domain optical coherence tomography (SD-OCT) criteria included a discrete, well-defined elevation of the RPE with a hyporeflective serous or a mixed reflective fibrovascular compartment. Pigment epithelial detachments had to demonstrate a focus of NV with angiography and SD-OCT. Clinical ophthalmoscopic examination and color fundus photography show a polyploidal choroidal vasculopathy lesions were excluded. Table 1 provides the full list of inclusion and exclusion criteria.

If both eyes of a patient were found to be eligible, then only one eye was selected to be included in the study. Patients did not undergo any form of intraocular surgery during the time of study.

Outcome Measures

The primary outcome was ETDRS BCVA at final follow-up of 12 months. Secondary outcome measures included the prevalence and volumetric measurements of specific morphologic features as seen on SD-OCT. These features included PED size (maximal height and volume), IRF, SRF, subretinal hyperreflective material (SRHRM), retinal thickness, geographic atrophy, and multilayering of fibrovascular material within PEDs. Ocular and systemic adverse events were also recorded.

Treatment Schedule

All study eyes received 6 monthly intravitreal injections of 2.0 mg/0.05 mL of aflibercept followed by 3 bimonthly injections. An additional 3 injections

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Table 1. Inclusion and Exclusion Criteria for the Study

Inclusion criteria
1. ≥50 years of age
2. Study eye contains a submacular fibrovascular PED ≤12 disk area
3. Central foveal involvement by the PED or NV related to AMD (NV maybe within or adjacent to the margin of PED)
4. ETDRS BCVA ≥19 letters and ≤73 letters (20/400–20/35)
5. Evidence of submacular fluid outside or surrounding the PED
Exclusion criteria
1. Any previous treatment for exudative AMD in the study eye
2. Previous periorbital therapeutic radiation
3. Previous RPE tear in the study eye
4. Previous ocular surgery (except laser capsulotomy) within past 90 days or anticipated surgery (except laser capsulotomy) within the next 12 months
5. Previous vitrectomy
6. Presence of any causes for NV and PED other than AMD
7. Presence of any substantial ocular disease (other than NV and PED) that may compromise vision and confound interpretation of data
8. Serous PED without NV and PCV lesions
9. Surface area of any submacular hemorrhage or fibrosis >50% of the PED
10. Active ocular infection during screening
11. IOP ≤25 mmHg with or without use of ocular hypotensive agents
12. Previous or current systemic anti-VEGF
13. Previous (within 90 days) or current oral or intravenous corticosteroid treatment
14. Sexually active men or women of child-bearing potential who are unwilling to practice contraception

IOP, intraocular pressure; PCV, polyploidal choroidal vasculopathy.

were allowed 1 month after the most recent injection on a pro re nata basis during the second 6-month period. Pro re nata features warranting injection included recurrence of IRF and/or SRF.

Assessment Schedule

A complete ocular examination, including ETDRS BCVA, biomicroscopic examination of the anterior segment and posterior pole of the retina, and indirect ophthalmoscopy of the retinal periphery, was performed for all patients. Spectral domain optical coherence tomography (Spectralis, Heidelberg Engineering, Heidelberg, Germany) using high-density scans was performed at baseline and then monthly for 12 months. Fluorescein angiography (Carl Zeiss Meditec, Dublin, CA) and color fundus photography (Carl Zeiss Meditec) were performed at baseline, 3 months, 6 months, and 12 months. Indocyanine green angiography (ICG; Carl Zeiss Meditec, Dublin, CA) was performed at baseline and 12 months.

Multimodal Imaging Assessments

All multimodal images including FA, ICG, and SD-OCT were sent to a third-party reading center (Doheny Image Reading Center [DIRC], Los Angeles, CA) for qualitative and quantitative measurements of NV, PEDs, and geographic atrophy. The grading protocol necessitated the grader to meticulously draw multiple boundaries on all OCT B-scans to manually segment the various structures of interest. The previously described and validated DIRC OCT grading software, OCTOR,[6,7] then applied a linear interpolation algorithm between the B-scans to generate volume and thickness maps. The foveal centers of all images were marked and ETDRS subfields were generated based on that foveal center for each SD-OCT. Additional qualitative review of the images was performed as part of the data analysis.

Image Analysis

After all data were collected, the PEDs were categorized into 3 groups: Type 1, Type 3, or mixed/other NV subtype based on analysis of their baseline SD-OCT, color fundus photography, FA, and ICG. Each case was classified according to the guidelines provided by Freund et al.[8] Type 1 NV was defined on SD-OCT as sub-RPE neovascular lesions associated with a PED comprised of vascular (heterogenous or multilayered reflectivity), serous (hyporeflective), or mixed components and on dye-based angiography as a hotspot associated with the PED or stippled late leakage with FA. Type 3 NV was identified on SD-OCT by the presence of a characteristic, intraretinal hyperreflective focus within the outer nuclear layer with or without associated IRF as described in previous articles[2,9–11] and confirmed by correlation with fundus photography showing a pinpoint intraretinal hemorrhage and FA and ICG showing a hotspot of angiographic leakage. Any eyes with more than 1 subtype of NV or Type 2 NV (classic, well-defined NV on FA or hyperreflective NV present within the subneurosensory compartment on SD-OCT) were excluded from analysis.

The presence of reticular pseudodrusen was evaluated by near infrared reflectance and SD-OCT. The presence of fibrovascular layering[12] and lipid bands within the PEDs, RPE tears, and geographic atrophy were also recorded.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2011 version 14 (Microsoft Corporation,

Redmond, WA) with SAS Add-In 6.1 for Microsoft Office and GraphPad QuickCalcs (http://www.graphpad.com/quickcalcs/). Differences between Type 1 and Type 3 NV were calculated using independent t-tests assuming unequal variances for scaled variables and Fisher exact tests for categorical variables. The paired *t*-test was used to compare scaled variables at baseline and final 12-month follow-up within each lesion group. Simple linear regression modeling was performed between SD-OCT morphologic features and baseline and final visual acuity. Two-tailed statistics was used for all calculations. Linear discriminant analysis was performed to evaluate the influence of baseline parameters on the development of geographic atrophy. Missing variables were not imputed. Statistical significance was set at 0.05.

Results

A total of 40 eyes from 40 patients were enrolled in the study from 3 centers. Four eyes were excluded from all analysis in this article because one demonstrated a vitelliform-like lesion not characteristic of AMD, one showed Type 2 lesion components, one had significant retinal distortion from an epiretinal membrane confounding analysis, and one showed Type 1 and Type 3 lesion components. Of the remaining 36 patients, 28 (78%) patients were found to have Type 1

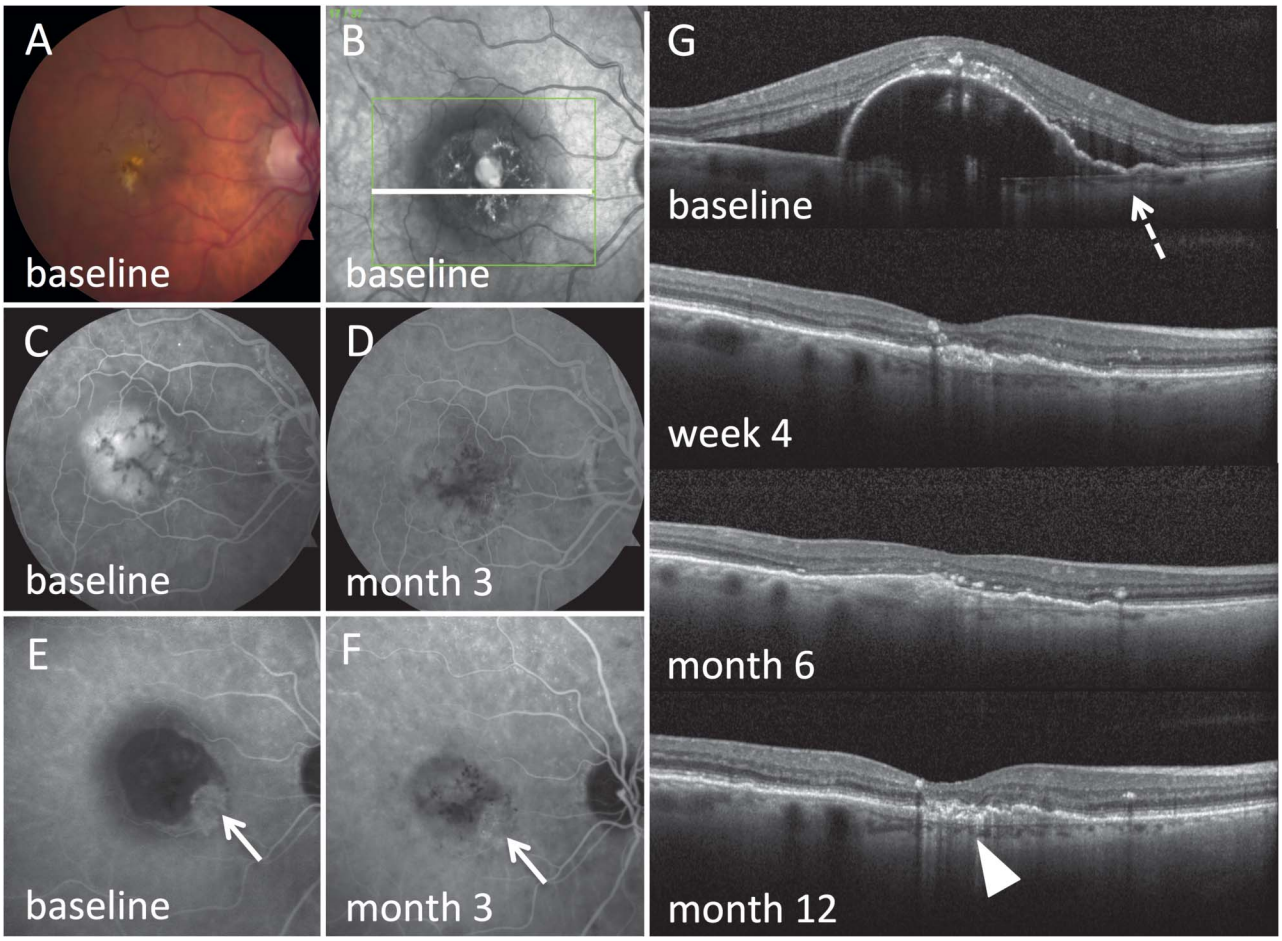

Fig. 1. Multimodal imaging of a PED due to Type 1 NV at baseline and at follow-up. **A.** Color fundus photography at baseline showed a PED in the absence of hemorrhage. **B.** Near-infrared image of the PED at baseline showed patches of hyperreflectivity over the PED. (**C**) Late FA at baseline demonstrated progressive pooling and leakage within the PED and blockage from speckled pigmentation. (**D**) Late FA at month 3 showed reduced PED pooling and leakage indicating regression of NV. (**E**) Indocyanine green angiography (ICG) at baseline demonstrated a neovascular complex at the nasal edge of the PED (arrow). (**F**) ICG at Month 3 showed increased staining within the PED with persistence of the nasal neovascular complex (arrow). (**G**) SD-OCT B-scans through the white line in (**B**) that cut through the nasal neovascular complex showed that the treatment-naive PED was largely serous with a Type 1 neovascular component at the nasal edge of the PED with associated RPE corrugations (dotted arrow) due to traction. With 1 injection, the PED collapsed (Week 4 and Month 6) and the SRF resolved. Note the onset of geographic atrophy over time as seen in Month 12 (arrow head).

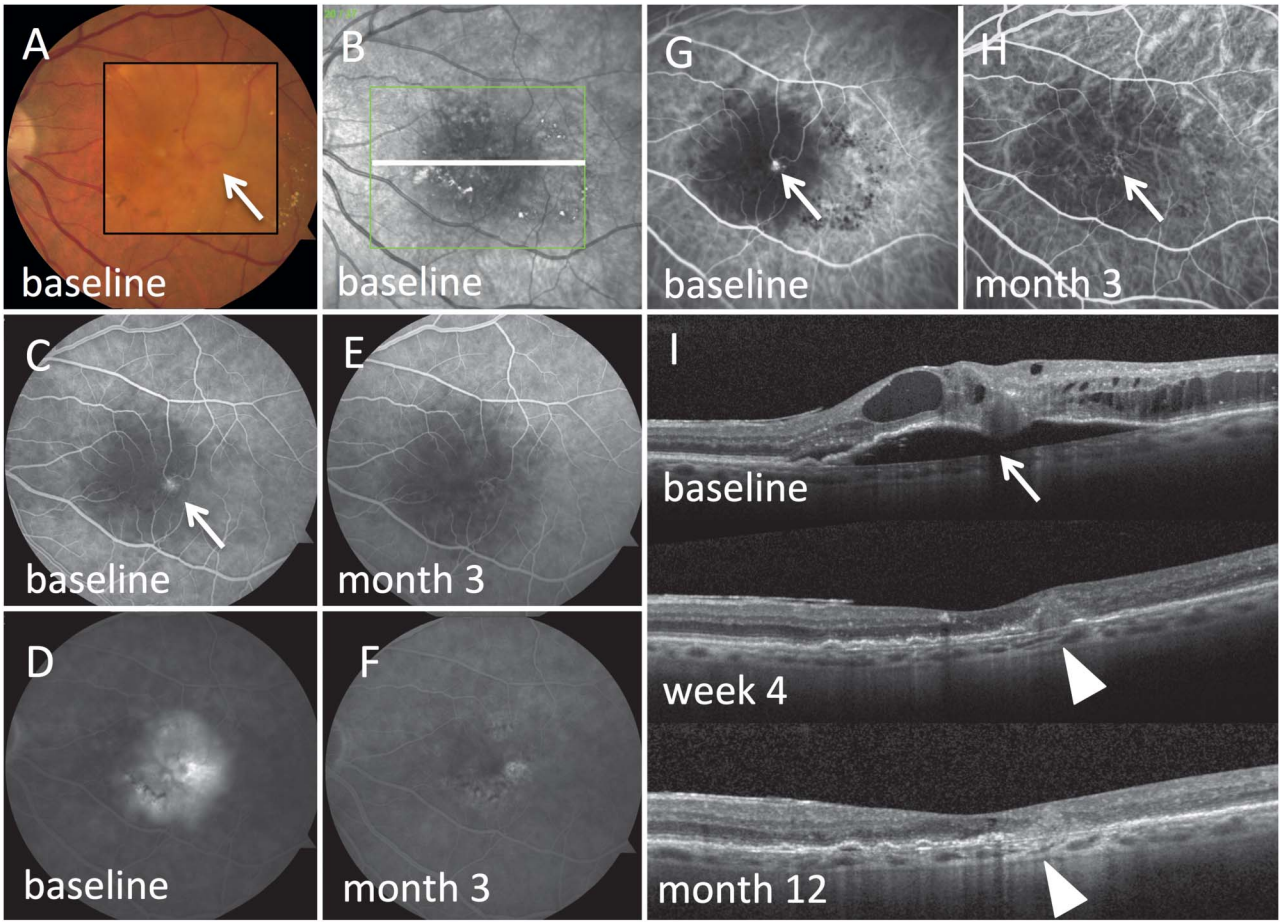

Fig. 2. Multimodal imaging of a PED due to Type 3 NV at baseline and at follow-up. At baseline, (**A**) color fundus photography showed exudates and a pinpoint hemorrhage (arrow) adjacent to an arteriole, and the (**B**) near-infrared image showed speckled hyperreflectance over the dark PED. **C.** The early FA demonstrated a hotspot (arrow) corresponding to the intraretinal neovascular complex and associated with the spot hemorrhage seen in (A), and (**D**) late FA frames showed diffuse pooling and leakage around the PED. **G.** Baseline indocyanine green angiography (ICG) also showed the hotspot (arrow). **I.** Baseline SD-OCT showed a hyperreflective focus corresponding to the intraretinal NV with associated IRF. With 1 injection, the PED collapsed and the IRF resolved which is clearly seen on with SD-OCT (Week 4); and with progressive injections, a small subretinal scar developed corresponding to the Type 3 lesion (**I**, arrow head, Week 4 and Month 12). Note the resolution of leakage on (**E**) early and (**F**) late FA and (**H**) ICG at the Month-3 interval.

lesions and 8 (22%) patients were found to have Type 3 lesions. Figure 1 and Figure 2 illustrate typical Type 1 and Type 3 lesions. The Type 1 group had 11 males and 17 females, and the Type 3 group had 2 males and 6 females ($P = 0.6820$). The Type 1 group had a mean age of 78 years (range 65–90), whereas the Type 3 group had a mean age of 84 years (range 67–98) ($P = 0.1110$). Table 2 illustrates the baseline characteristics by neovascular subtype.

Three patients (2 Type 1 lesions and 1 Type 3 lesion) did not complete the study and were excluded for all analysis requiring longitudinal data beyond their last visit. Five Type 1 eyes developed RPE tears (3 grade 3 tears after 1, 4, and 5 injections and 2 grade 4 tears both after 1 injection), whereas none of the Type 3 eyes developed RPE tears. These 5 eyes with RPE tears were analyzed as a separate group from the remaining Type 1 lesions.

Table 2. Baseline Demographics and Vision of All Included Eyes Separated by NV Type

	All Patients (n = 36)	Type 1 (n = 28)	Type 3 (n = 8)	*P*
Age, years	80 ± 8.0	78 ± 6.8	84 ± 11	0.1110
Sex	23 F	17 F	6 F	0.6820
	13 M	11 M	2 M	
BCVA (ETDRS)	59 ± 8.9 (Snellen 20/66)	60 ± 8.7 (Snellen 20/63)	56 ± 9.7 (Snellen 20/76)	0.1780

There was no statistical difference in baseline demographics or vision for Type 1 and Type 3 patients. There was an overall greater presence of females in both groups, consistent with the AMD populations.

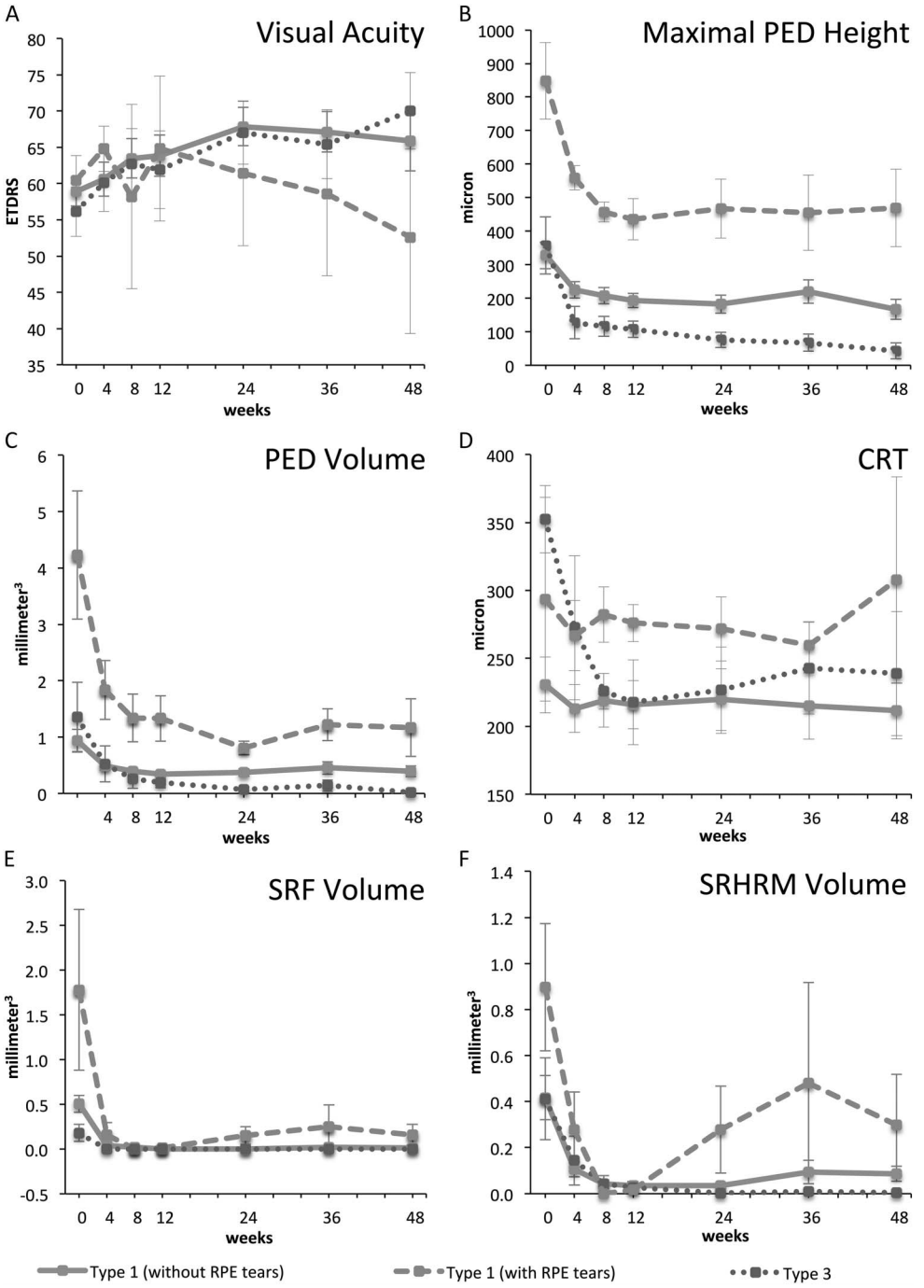

Fig. 3. Functional and anatomical outcomes over time for Type 1 lesions that did not develop RPE tears, Type 1 lesions that developed RPE tears, and Type 3 lesions. **A.** Both Type 1 eyes without RPE tears and Type 3 eyes showed vision improvement from baseline to final 12-month follow-up; however, Type 3 eyes showed a 9.2 greater letter gain in vision. By contrast, Type 1 eyes with RPE tears showed a vision decrease with a greater SD. (**B** and **C**) Maximal PED height and PED volume both showed decreases in all 3 groups over time. Type 1 eyes without RPE tears and Type 3 eyes had similar baseline PED sizes; however, given the greatest decrease over time for Type 3 eyes, the Type 3 group demonstrated a smaller 12 months PED size. Type 1 eyes with RPE tears, however, showed a greater PED size at all time points. **D.** Type 3 eyes had a higher CRT than Type 1 eyes at baseline but showed a significant decrease within 8 weeks. Type 1 eyes with RPE tears had a consistently greater average CRT compared with Type 1 eyes that never experienced an RPE tear; however, the difference at baseline and final 12-month follow-up was not significant likely because of the small sample size and the high variation within the group without RPE tears. **E.** Type 1 eyes with RPE tears had the greatest initial total SRF volume and Type 3 eyes had the least SRF volume. All 3 groups showed a decrease in SRF volume over time, but and Type 1 eyes without RPE tears and Type 3 eyes showed a quick reduction toward 0. **F.** Baseline SRHRM was greater for Type 1 eyes with RPE tears, which showed an initial average decrease followed by an increase. The Type 1 eyes without RPE tears and Type 3 eyes all began with similar total SRHRM volume and both showed a rapid decrease with time. Error bars represent SE.

Visual Acuity Analysis

The baseline ETDRS BCVA ± SD was 59 ± 8.9 letters (Snellen 20/66) for all lesions, 60 ± 8.7 letters (Snellen 20/63) for Type 1 lesions, and 56 ± 9.7 letters (Snellen 20/76) for Type 3 lesions (P = 0.1780).[13] The BCVA at final 12-month follow-up was 65 ± 27 letters (Snellen 20/50) for all lesions, 64 ± 27 letters (Snellen 20/53) for Type 1 lesions, and 70 ± 28 letters (Snellen 20/40) for Type 3 lesions (P = 0.1971 between Type 1 and Type 3 lesions, including eyes with RPE tears but excluding those who did not finish the study).

At final 12-month follow-up, all eyes showed a 6.5 ± 22 letters improvement. Type 1 eyes showed an overall improvement of 4.5 ± 23 letters (P = 0.1665) and an improvement of 7.5 ± 19 letters in

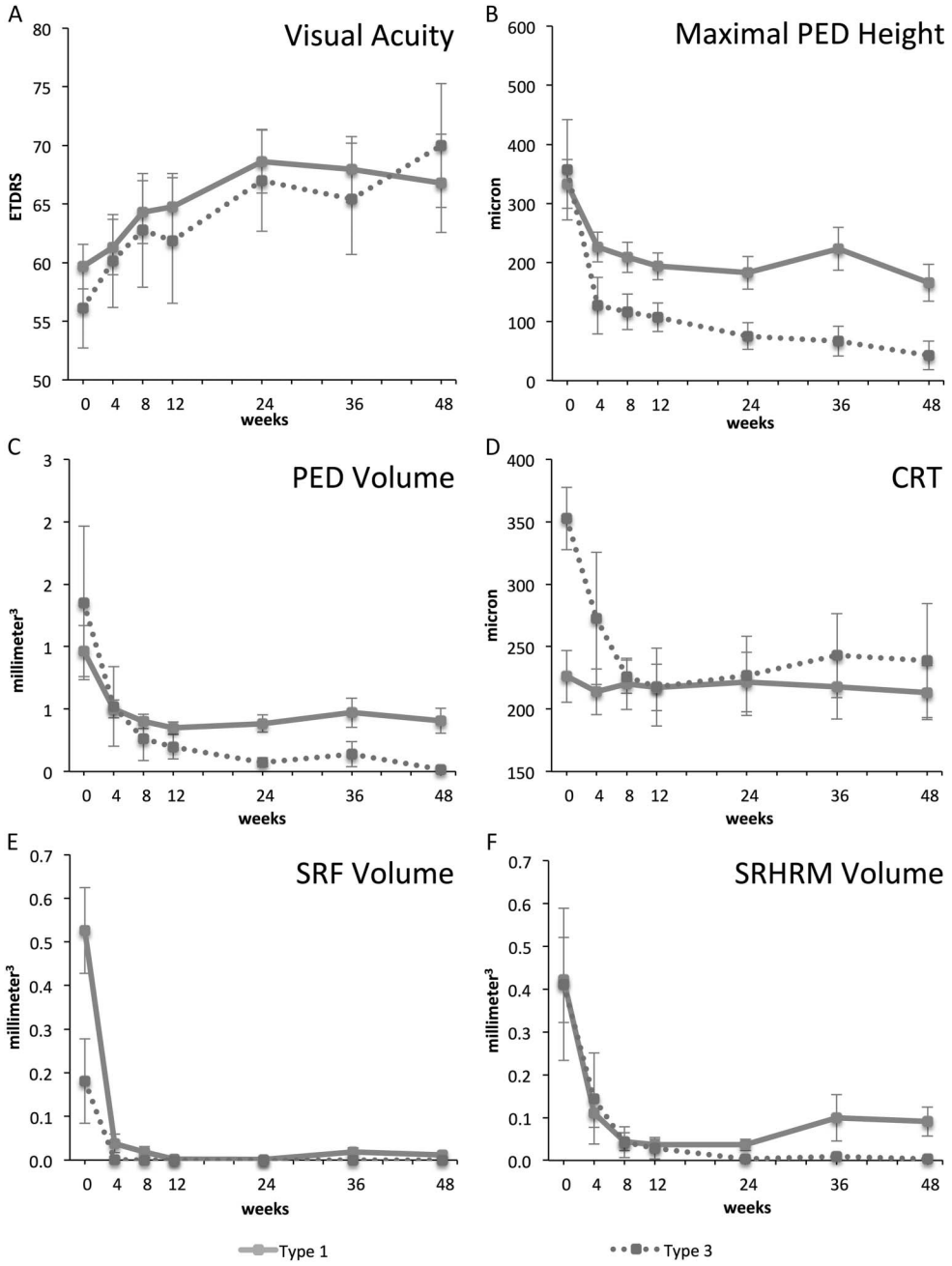

Fig. 4. Functional and anatomic outcomes over time for all Type 1 lesions versus Type 3 lesions. The green line represents all 28 Type 1, solid lesions, and the red, dotted line represents all 8 Type 3 lesions. All trends for Type 1 lesions are similar to the trends in Type 1 lesions without RPE tears illustrated in Fig. 3. **A.** Type 1 lesions showed an overall improvement of 4.5 ± 23 letters, and Type 3 lesions showed an improvement of 14 ± 11 letters. There was no statistically significant difference at baseline or final BCVA between the 2 groups ($P = 0.1780$ for baseline, $P = 0.1971$ for final 12-month follow-up). Additionally, Type 1 lesions did not show a statistically significant change in vision ($P = 0.1665$). (**B** and **C**) All Type 1 lesions showed a statistically significant decrease in PED size from baseline to final follow-up ($P = 0.0001$ for PED maximal height, $P = 0.0008$ for PED volume) and a statistically significant difference from Type 3 lesions at final follow-up ($P = 0.0005$ for PED maximal height, $P = 0.0008$ for PED volume). **D.** CRT was statistically different at baseline between Type 1 and Type 3 eyes ($P = 0.0009$) but not different at final follow-up ($P = 0.3436$). Type 1 eyes did not show a statistically significant change in CRT from baseline to final follow-up, whereas Type 3 eyes showed a significant decrease. **E.** The 2 lesion groups showed a significant difference at baseline ($P = 0.0059$) and follow-up ($P = 0.0501$) for SRF volume. The aggregate Type 1 group also showed a decrease in SRF volume ($P = 0.0008$). (**F**) SRHRM volume was statistically different at final follow-up between Type 1 and Type 3 ($P = 0.0108$) given the significant decrease in Type 1 eyes ($P = 0.0036$) and Type 3 ($P = 0.0419$) eyes.

the group of eyes that did not develop a RPE tears ($P = 0.0454$) and a decrease of 7.8 ± 37 letters in the group of eyes that developed a tear ($P = 0.3292$). Type 3 lesions showed an improvement of 14 ± 11 letters ($P = 0.0072$). Type 3 lesions had an overall 9.2 greater gain in ETDRS letters at the conclusion of the study as compared with the Type 1 lesion group with a P value of 0.0734. Figures 3 and 4 show the visual acuity trends throughout the study.

Spectral Domain Optical Coherence Tomography Analysis

Baseline SD-OCT characteristics between the lesion types are outlined in Table 3. Notable differences that reached statistical significance between Type 1 and Type 3 lesions included the greater presence of IRF, DCP exudates, and reticular pseudodrusen in Type 3 lesions at baseline. Type 1 lesions showed a trend toward greater presence of SRF and multilayering at baseline.

Table 3. Baseline Qualitative Morphologic Components of All Eyes Separated by NV Type

	Type 1 (n = 28), %	Type 3 (n = 8)	*P*
IRF	8 (29)	8 (100)	0.0004*
DCP exudates	3 (11)	8 (100)	<0.0001*
SRF	26 (93)	5 (63)	0.0615†
Center-involving	14 (54)	1 (20)	0.3326
Eccentric-only	12 (46)	4 (80)	
SRHRM	23 (82)	7 (88)	1.000
Lipid bands	2 (7)	2 (25)	0.2075
Reticular pseudodrusen	3 (11)	6 (75)	0.0010*
Serous component in PED	16 (57)	7 (88)	0.2125
Multilayering in PED	10 (36)	0 (0)	0.0756†

The presence of IRF, DCP exudates, SRF, SRHRM, lipid bands, and PED contents were determined based on the SD-OCT. Reticular pseudodrusen was determined through near-infrared images and SD-OCT. Deep retinal capillary plexus exudates were defined as hyperreflective foci centered at the level of the inner nuclear layer, and SRHRM was defined as hyperreflective material located external to the retina and internal to the retinal pigment epithelial layer.

*Statistical significance.

†Statistical trends.

As illustrated in Table 4, at baseline, central retinal thickness (CRT) (226 ± 99 μm for Type 1 without RPE tears, 294 ± 168 μm for Type 1 with RPE tears, 352 ± 70 μm for Type 3) was significantly greater with Type 3 lesions, and SRF volume (0.53 ± 0.47 mm^3 for Type 1 without RPE tears, 1.8 ± 2.0 mm^3 for Type 1 with RPE tears, and 0.18 ± 0.27 mm^3 for Type 3) was statistically greater with Type 1 lesions.

At 12-month follow-up, CRT (213 ± 99 μm for Type 1 without RPE tears, 308 ± 170 μm for Type 1 with RPE tears, and 239 ± 112 μm for Type 3) remained greater in Type 3 eyes as compared with Type 1 eyes without RPE tears, but SRF volume (0.012 ± 0.024 mm^3 for Type 1 without RPE tears, 0.16 ± 0.26 mm^3 for Type 1 with RPE tears, and 0 mm^3 for Type 3), maximal PED height (166 ± 144 μm for Type 1 without RPE tears, 469 ± 258 μm for Type 1 with RPE tears, and 43 ± 59 μm for Type 3), PED volume (0.41 ± 0.46 mm^3 for Type 1 without RPE tears, 1.2 ± 1.1 mm^3 for Type 1 with RPE tears, and 0.017 ± 0.024 mm^3 for Type 3), and SRHRM volume (0.091 ± 0.16 mm^3 for Type 1 without RPE tears, 0.30 ± 0.49 mm^3 for Type 1 with RPE tears, and 0.0033 ± 0.0071 mm^3 for Type 3) were all statistically greater with Type 1 eyes without RPE tears than Type 3 eyes.

Additionally, at baseline, Type 1 eyes with RPE tears had a significantly greater maximal PED height (333 ± 199 μm for Type 1 without RPE tears and 849 ± 256 μm for Type 1 with RPE tears), a significantly greater PED volume (0.97 ± 0.99 mm^3 for Type 1 without RPE tears and 4.2 ± 2.5 mm^3 for Type 1 with RPE tears), and a trend toward greater SRHRM volume (0.42 ± 0.47 mm^3 for Type 1 without RPE tears and 0.90 ± 0.62 mm^3 for Type 1 with RPE tears) than Type 1 lesions that did not sustain tears.

Within each lesion group, both Type 1 and Type 3 lesions showed a statistically significant decrease from baseline in the maximal PED height ($P = 0.0010$ for Type 1 without RPE tears, $P = 0.0320$ for Type 1 with RPE tears, and $P = 0.0060$ for Type 3) and PED volume ($P = 0.0054$ for Type 1 without RPE tears, $P = 0.0133$ for Type 1 with RPE tears, and $P = 0.0112$ for Type 3). Additionally, the final SRHRM volume showed a decrease from baseline for Type 1 without RPE tears and Type 3 lesions ($P = 0.0088$ for Type 1 without RPE tears, $P = 0.1223$ for Type 1 with RPE tears, and $P = 0.0419$ for Type 3). For CRT, Type 3 lesions showed a statistically significant decrease from baseline, whereas Type 1 lesions did not ($P = 0.1208$ for Type 1 without RPE tears, $P = 0.4528$ for Type 1 with RPE tears, and $P = 0.0073$ for Type 3). Type 1 lesions without RPE tears showed a statistically significant decrease in SRF volume from baseline, whereas Type 1 lesions with RPE tears and Type 3 lesions showed a trend in decrease ($P < 0.0001$ for Type 1 without RPE tears, $P = 0.0778$ for Type 1 with RPE tears, and $P = 0.0605$ for Type 3). Table 4 summarizes the differences between the groups, and Figure 3 and Figure 4 illustrate the anatomical trends.

Five of 28 (18%) Type 1 lesions had a hyperreflective focus above the RPE layer similar to Type 3 lesions except that there was no associated disruption of the RPE or disorganization of the inner retina. Figure 5 shows these 5 "pseudo-hyperreflective focus" and the 8 Type 3 lesions in comparison.

Twenty-one of 28 (75%) Type 1 eyes showed RPE corrugations that were eccentric, central, or diffusely distributed on top of the PED, whereas 4 of 8 (50%) Type 3 eyes displayed RPE corrugations most of which were all diffusely distributed ($P = 0.2137$).

Multilayering Within Pigment Epithelial Detachments

Ten of 28 (36%) Type 1 PEDs showed multilayering at baseline, whereas none of the Type 3 lesions showed this feature ($P = 0.0756$).[12] By the conclusion of the study, 9 additional Type 1 eyes developed layering including the 2 eyes that did not complete the study, whereas none of the Type 3 eyes ever developed this feature ($P = 0.0017$). All eyes that developed RPE tears failed to demonstrate any layering at baseline or follow-up. Type 1 eyes that had or developed multilayering

Table 4. Differences in Visual Acuity and Morphologic Characteristics of Type 1 and Type 3 Lesions From Baseline to Final 12-Month Follow-Up

	Baseline	12 Months	*P*
BCVA (ETDRS)			
Type 1 without RPE tears (ETDRS)	60 ± 9.1	67 ± 19	0.0454*
Type 1 with RPE tears (ETDRS)	60 ± 7.7	53 ± 30	0.3292
Type 3 (ETDRS)	56 ± 9.7	70 ± 14	0.0072*
P			
Type 1 without RPE tears vs. Type 3	0.1924	0.3197	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.4274	0.1791	
Maximal PED height			
Type 1 without RPE tears μm	333 ± 199	166 ± 144	0.0010*
Type 1 with RPE tears μm	849 ± 256	469 ± 258	0.0320*
Type 3 μm	357 ± 240	43 ± 59	0.0060*
P			
Type 1 without RPE tears vs. Type 3	0.3996	0.0032*	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.0043*	0.0286*	
PED volume			
Type 1 without RPE tears (mm^3)	0.97 ± 0.99	0.41 ± 0.46	0.0054*
Type 1 with RPE tears (mm^3)	4.2 ± 2.5	1.2 ± 1.1	0.0133*
Type 3 (mm^3)	1.4 ± 1.7	0.017 ± 0.024	0.0112*
P			
Type 1 without RPE tears vs. Type 3	0.2850	0.0008*	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.0221*	0.1065	
Mean CRT			
Type 1 without RPE tears μm	226 ± 99	213 ± 99	0.1208
Type 1 with RPE tears μm	294 ± 168	308 ± 170	0.4528
Type 3 μm	352 ± 70	239 ± 112	0.0073*
P			
Type 1 without RPE tears vs. Type 3	0.0005*	0.0215*	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.2115	0.1412	
SRF volume			
Type 1 without RPE tears, mm^3	0.53 ± 0.47	0.012 ± 0.024	<0.0001*
Type 1 with RPE tears, mm^3	1.8 ± 2.0	0.16 ± 0.26	0.0778†
Type 3, mm^3	0.18 ± 0.27	0	0.0605†
P			
Type 1 without RPE tears vs. Type 3	0.0102*	0.0299*	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.1182	0.1313	
SRHRM Volume			
Type 1 without RPE tears, mm^3	0.42 ± 0.47	0.091 ± 0.16	0.0088*
Type 1 with RPE tears, mm^3	0.90 ± 0.62	0.30 ± 0.49	0.1223
Type 3, mm^3	0.41 ± 0.50	0.0033 ± 0.0071	0.0419*
P			
Type 1 without RPE tears vs. Type 3	0.4802	0.0168*	
Type 1 without RPE tears vs. Type 1 with RPE tears	0.0834†	0.2011	

*Statistical significance.
†Statistical trend.

had a 5.3 ± 19 letter gain, which was not found to be different from eyes without layering that had a 3.3 ± 29 letter gain overall ($P = 0.4455$) and a 14 ± 13 letter gain ($P = 0.3425$) when excluding eyes with RPE tears. Figure 6 illustrates the development of the multilayering feature in a typical Type 1 eye with PED, and Table 5 summarizes the prevalence of the feature.

Geographic Atrophy Analysis

The presence of geographic atrophy was identified on color photography, near-infrared, and SD-OCT. The atrophy area was calculated using SD-OCT. None of the eyes with Type 1 lesions demonstrated geographic atrophy at baseline, but 15 of 26 (58%) eyes with Type 1 lesions developed geographic atrophy by the end of the study, including all 5 eyes that sustained RPE tears. For Type 3 eyes, 1 of 8 (12.5%) had geographic atrophy at baseline and 6 out 8 (75%) eyes displayed atrophy by the end of the study. Patients who did not finish the study and did not develop atrophy before their last visit were not included in this subanalysis. Interestingly, Type 3 eyes that had or developed geographic atrophy still had a gain of 16 ± 11 letters

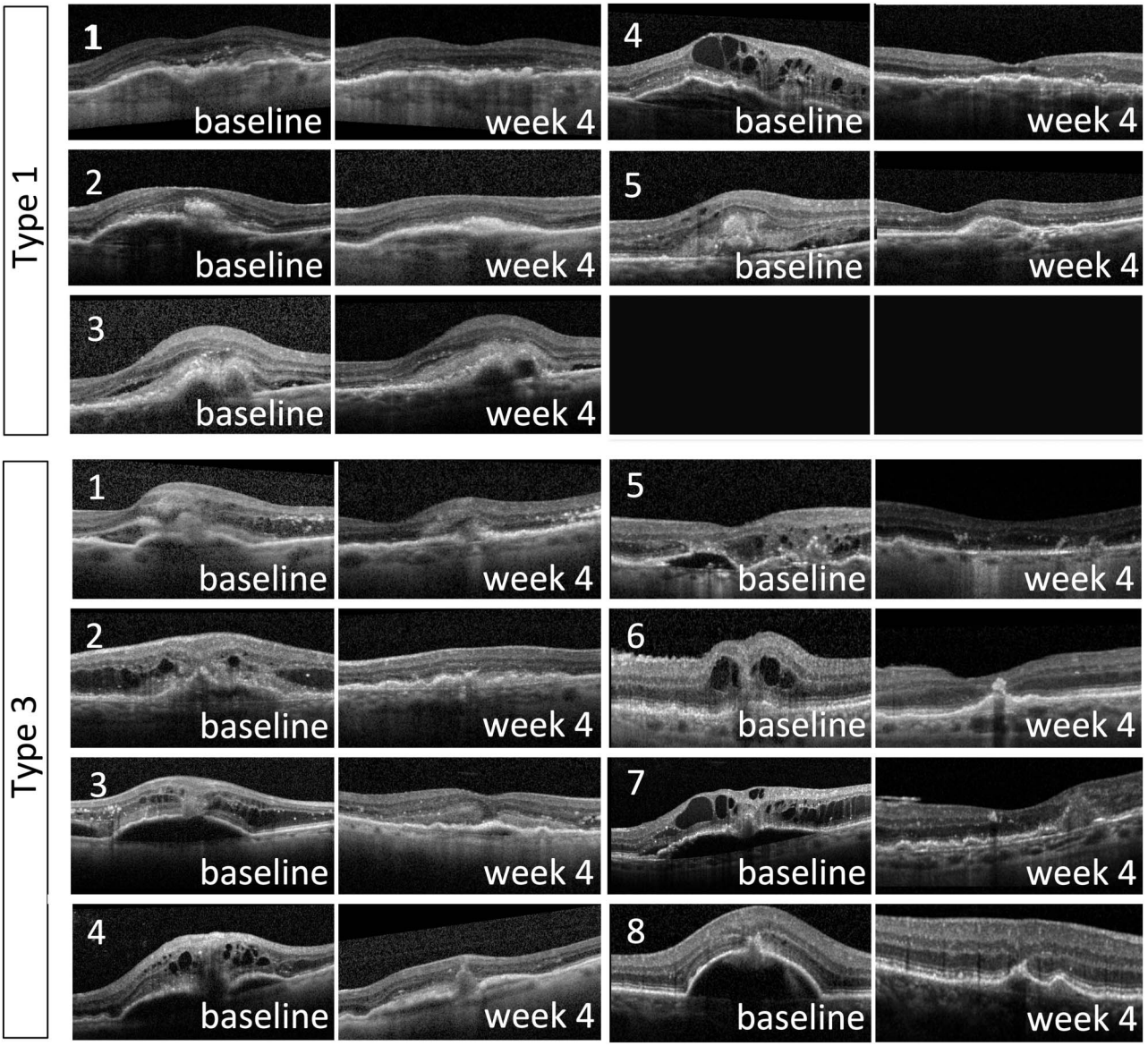

Fig. 5. Hyperreflective foci in Type 1 and Type 3 lesions as seen on SD-OCT. In 5 of the Type 1 lesions, a focus of hyperreflectivity above the RPE that mimicked a Type 3 neovascular complex could be identified. However, as opposed to Type 3 lesions, these "pseudo" hyperreflective foci resolved rapidly with anti-VEGF therapy and without the subsequent scarring or disruption of the outer retina and/or RPE. These 5 lesions are illustrated in comparison with the 8 Type 3 lesions. Careful examination of SD-OCT is needed to distinguish atypical appearing Type 1 lesions from Type 3 lesions.

compared with Type 1 eyes that showed a decrease of 2.4 ± 28 letters ($P = 0.0398$). Type 1 and Type 3 eyes that never developed geographic atrophy showed similar letter gains (14 ± 9.8 letters for Type 1 and 7.5 ± 13 letters for Type 3, $P = 0.3637$). Table 5 summarizes the prevalence of geographic atrophy. At final 12-month follow-up, the area of geographic atrophy was 0.328 ± 0.236 mm^2 in Type 1 lesions, excluding eyes with RPE tears, and 0.324 ± 0.287 mm^2 in Type 3 lesion ($P = 0.973$). Linear discriminant analysis was performed to evaluate the influence of baseline PED size, SRF volume, and SRHRM volume on the development of geographic atrophy in Type 1 and Type 3 lesions. Only SRHRM volume was positively correlated with atrophy development in Type 3 lesions ($P = 0.0260$).

Anatomic Predictors of Visual Acuity

At baseline, only 8 of 28 (29%) Type 1 eyes had IRF, whereas all Type 3 eyes had IRF. The baseline BCVA in these Type 1 eyes with IRF was 55 ± 11 letters (Snellen 20/80), whereas the remaining 20 eyes without IRF had a baseline BCVA of 62 ± 7.2 letters (Snellen 20/63) ($P = 0.0745$). At final 12-month

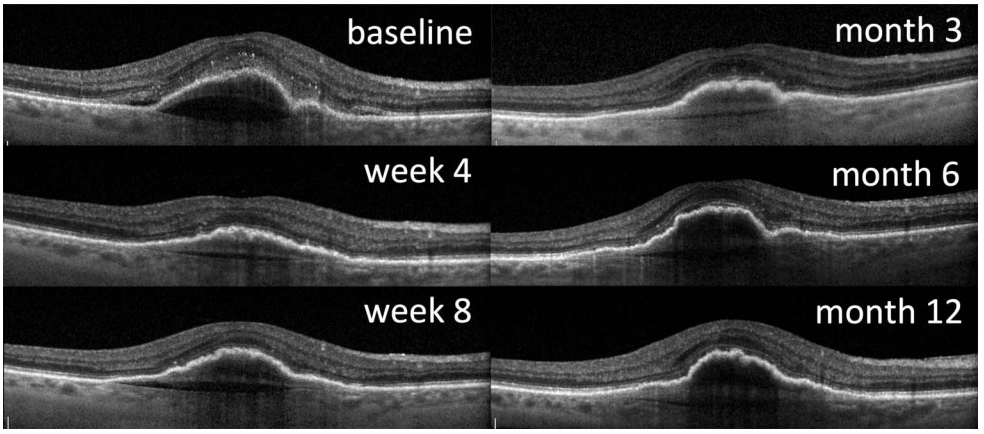

Fig. 6. Spectral domain optical coherence tomography evolution of a multilayered PED in an eye with Type 1 NV. At baseline, the treatment-naive PED harbored serous and fibrovascular material within the sub-RPE compartment with overlying SRHRM SRF. With 1 injection, there was a remarkable reduction in the PED and associated SRHRM (Week 4). At subsequent time intervals (Week 8 and Month 3), the PED matured and a laminar structure developed within the PED above a prechoroidal cleft separating the PED contents from the underlying choroid and Bruch membrane. At Months 6 and 12, some recurrence of serous fluid was seen within the laminar structure with slight enlargement of the PED. This multilayering feature was progressive in nature and can be seen in chronic Type 1 PEDs.

follow-up, 7 of 26 (27%) Type 1 eyes, including all 5 eyes with RPE tears, and 3 of 7 (43%) Type 3 eyes had residual IRF. Those Type 1 eyes with IRF had a final BCVA of 57 ± 26 letters and those without IRF had a final BCVA of 67 ± 28 letters (P = 0.4024). For Type 1 eyes that began with IRF, their final BCVA at 12 months was 57 ± 20 letters, whereas those that began without IRF had a final BCVA of 67 ± 29 letters (P = 0.3703).

At baseline, 26 of 28 (93%) Type 1 and 5 of 8 (63%) Type 3 eyes had SRF. At final 12-month follow-up, 8 of 26 (31%) Type 1 eyes, including 3 with RPE tears, and none of the Type 3 eyes had residual SRF. At baseline, Type 1 eyes showed a trend toward worse vision with SRF (59 ± 8.9 letters with SRF, 66 ± 3.5 letters without SRF, P = 0.0849), and Type 3 eyes showed a statistically significantly lower BCVA for eyes with SRF (51 ± 6.7 letters with SRF, 64 ± 8.6 letters without SRF, P = 0.04827). At final 12-month follow-up, Type 1 eyes with SRF did not show a worse vision than those with SRF (66 ± 23 letters with SRF, 63 ± 28 letters without SRF, P = 0.1838). Additionally, Type 1 and Type 3 eyes that began with baseline SRF did not show worse final vision than those that began without SRF (Type 1: 63 ± 25 with SRF, 85 ± 60 letters without SRF, P = 0.3708; Type 3: 64 ± 24 letters with SRF, 84 ± 49 letters without SRF, P = 0.3973).

At baseline, 14 of 26 (54%) of Type 1 eyes with SRF had subfoveal involvement, whereas only 1 of 5 (20%) of Type 3 eyes with SRF did. Type 1 eyes with subfoveal fluid did not have a statistically significant different baseline BCVA as compared with eyes with eccentric-only fluid (59 ± 10 letters for subfoveal involvement, 60 ± 8.2 for eccentric only, P = 0.3338). Simple linear regression models were run between BCVA at baseline and final 12-month follow-up with PED volume, PED maximal height, CRT, mean central SRF thickness, SRF volume, and SRHRM volume for all Type 1 lesions, Type 1 lesions excluding RPE tears and Type 3 lesions. The only anatomical feature that was able to predict BCVA with statistical significance was final CRT for Type 1 lesions excluding RPE tears (P = 0.0185). Simple linear regression was also performed between baseline and final BCVA and was not found to be predictive.

Number of Injections to Achieve Dry State

Of the 33 of 36 patients (26 with Type 1 lesion and 7 with Type 3 lesion) who finished the study, 4 eyes with Type 1 lesions never achieved complete regression of macular edema and/or SRF with our injection regimen. Of those eyes that did achieve complete regression, the average number of injections required to induce a dry state was 1.636 (range, 1–4 injections) for Type 1 lesions and 1.143 (range, 1–2 injections) for Type 3 lesions (P = 0.0251). Five of these 22 (23%) Type 1 eyes subsequently had recurrence of fluid, whereas 2 of 7 (29%) Type 3 eyes had recurrence (P = 1.000). Three of the 4 (75%) Type 1 eyes that never achieved a dry state and 2 of 5 (40%) Type 1 eyes that had recurrence of fluid sustained RPE tears and had persistent IRF at the edge of the tear. Additionally, 79% of Type 1 eyes required one or more pro re nata injections in the latter half of the study, whereas only 20% of Type 3 eyes did (P = 0.0223).

Discussion

In this prospective investigation, the baseline anatomical characteristics of treatment-naive eyes with neovascular AMD and PED due to Type 1 or Type 3 NV and the 1-year visual and anatomical response to intravitreal aflibercept injections were studied. In

Table 5. Presence of RPE Tears, Multilayering, and Geographic Atrophy at Baseline and Final 12 Month Follow-Up Separated by NV Type

	Baseline			12 Months		
	Type 1	Type 3	*P*	Type 1	Type 3	*P*
RPE tears	0/28 (0%)	0/8 (0%)	1.0000	5/26 (19%)	0/7 (0%)	0.5612
Multilayered PED	10/28 (36%)	0/8 (0%)	0.0756*	19/28† (68%)	0/7‡ (0%)	0.0017§
Geographic atrophy	0/28 (0%)	1/8 (12.5%)	0.2432	15/26¶ (58%)	6/8** (75%)	0.4438

All eyes with RPE tears occurred in Type 1 eyes. There was a statistically significant greater prevalence of multilayering in Type 1 compared with Type 3 eyes at final follow-up and a trend at baseline. More GA was seen in Type 3 eyes than in Type 1 eyes, but that result did not reach statistical significance at baseline or follow-up.

*Statistical trends.

†The eyes of the 2 patients with Type 1 lesions who did not finish the study began developing multilayering before being lost to follow-up.

‡The eye of the single Type 3 patient who did not finish the study did not develop multilayering before being lost to follow-up. As a result, we cannot be certain that the eye would not have developed layering at 12 months, so that eye is not included in this subanalysis.

§Statistical significance.

¶The 2 eyes with Type 1 lesions that did not finish the study did not develop GA before being lost to follow-up. As a result, we cannot be certain that the eye would not have developed atrophy at 12 months, so those eyes were not included in this subanalysis.

**The eye of the single patient 1 eye with Type 3 lesions that did not finish the study developed GA before conclusion of the study and was included.

GA, geographic atrophy.

a consecutive group of 266 eyes with newly diagnosed neovascular AMD, Jung et al[3] found a significantly older patient population with Type 3 NV compared with other neovascular subtypes, which is similar to our data that showed that Type 3 patients were on average 5.6 years older than Type 1 patients. Our study also noted a predominant female population with both lesion subtypes but especially in Type 3 NV, which is consistent with previous articles.[14]

In their cohort, Jung et al noted that 40% of all lesions in were Type 1, whereas 34% were Type 3 and 17% were mixed lesions. The remaining lesions were Type 2 (9%).[3] In a separate study, Marsiglia et al found that 47% of unilateral treatment-naive eyes with neovascular AMD harbored Type 1 lesions and 24% harbored Type 3 lesions.[15] Our study found a distribution of 74% (28/38) with Type 1 lesions, and 21% (8/38) with Type 3 lesions, 2.6% (1/38) with mixed lesions, and 2.6% (1/38) with Type 2 lesion. The greater proportion of Type 1 lesions in our series may be related to our moderate sample size. Moreover, baseline lesion components may vary to a certain extent for amongst different study populations, and we included only one eye from each patient, whereas Jung et al had 35 patients with bilateral disease.

Functionally, our patients demonstrated an overall gain of 6.5 ± 22 letters, with a 4.5 ± 23 letter gain in Type 1 eyes and a 14 ± 11 letter gain in Type 3 eyes. Both groups exhibited statistically significant improvements in vision, but eyes with Type 3 lesions demonstrated a 9.2 greater letter gain than eyes with Type 1 lesions. Previous studies have shown similar visual acuity improvements. In a retrospective study of PEDs associated with treatment-naive AMD, 3 loading doses of intravitreal aflibercept injections resulted in a mean vision gain of 9.3 letters.[16] Another retrospective study showed a 7-letter gain after the same aflibercept-loading regimen.[17]

In our study, slightly more Type 3 eyes developed GA than Type 1 eyes (58% for Type 1 and 75% for Type 3), and both groups had similar atrophic areas (0.328 ± 0.236 mm^2 for Type 1 and 0.324 ± 0.287 mm^2 for Type 3). However, Type 3 eyes NV with GA still experienced a gain of 16 ± 11 letters, whereas Type 1 with GA eyes showed a decrease of 2.4 ± 28 letters. In summary, visual gain was significantly greater in eyes with Type 3-associated PED even with the development of geographic atrophy. An explanation of this finding is unclear, but Type 3 lesions may be more responsive to anti-VEGF therapy as the lesions are located intraretinally and originate from a different vascular network than Type 1 lesions, which have a more occult location under the RPE and originate from the larger choroidal vascular plexus. Additionally, because Type 3 lesions appears to originate from the DCP of the parafoveal region,[8,11] subsequent was, therefore, rarely central at onset, whereas Type 1 lesions were often subfoveal. Additionally, although we evaluated a number of potential factors, only the presence of baseline SRHRM in Type 3 eyes as served as a predictive factor for atrophy. Interestingly, PED size does not seem to be a predictive factor for atrophy development.

At baseline, the mean PED size was similar for Type 1 and Type 3 NV, except for the Type 1 eyes that developed RPE tears; this latter group had a much greater baseline PED maximal height and volume (849 ± 256 μm for PED maximal height, 4.2 ± 2.5 mm^3 for PED volume). Type 3 lesions had a significantly higher rate of IRF, DCP exudates and reticular pseudodrusen,

and greater CRT, whereas Type 1 lesions had an higher rate of SRF with greater SRF volume and a greater rate of PED multilayering at baseline. Although these characteristics of Type 1 and Type 3 lesions have been previously described,[2,3,8,18] to the best of our knowledge, our study is the first to directly compare the prevalence and quality of these features between Type 1 and Type 3 eyes and to prospectively study their comparative response to treatment. Both Type 1 and Type 3 lesions showed a decrease in maximal PED height, PED volume, and SRHRM. Additionally, Type 3 lesions showed a statistically significant decrease in CRT, whereas Type 1 lesions did not. Note that Type 1 lesions had minimal IRF at baseline in contrast to Type 3 lesions. Type 1 lesions showed a statistically significant decrease in SRF volume, whereas Type 3 lesions showed only a reduction trend. The origin and pathogenesis of Type 1 and Type 3 NV may explain these disparate clinical findings.

The significant association of IRF and middle layer exudates at the level of the DCP with Type 3 NV is not at all surprising. Type 3 NV is known to originate at the DCP, likely driven by various ischemic mechanisms in the parafoveal middle retina, which is a water-shed-like zone particularly prone to hypoxic injury.[19,20] The presence of IRF and DCP exudates, which invariably develops in association with the intraretinal portion of the Type 3 lesions, is therefore a consequence of leaky intraretinal NV. Additionally, outer retinal and choroidal ischemia has been described to drive the Type 3 neovascularization process.[21] Accordingly, we found an increased rate of reticular pseudodrusen, which has been associated with choroidal ischemia in eyes with Type 3 NV consistent with a study by Marsiglia et al.[15]

Type 1 lesions, however, originate from the choroid without an intraretinal component. Therefore, in the absence of intraretinal NV, IRF is unusual especially with early Type 1 lesions. However, outer retinal and RPE disruption associated with more mature or chronic Type 1 lesions can lead to accumulation of IRF and has been correlated with a worse visual prognosis.[8] Of note, our study found that Type 1 eyes with IRF at baseline had a trend toward lower BCVA than that of eyes without IRF likely because of more chronic or advanced Type 1 lesions. This difference was maintained at the final 12-month follow-up visit; however, with the increase in the range of visual acuity, this difference was not found to be statistically significant. Additionally, CRT was greater in Type 3 PED eyes both at baseline and at the final 12-month follow-up; and although both subtypes showed improvement in retinal thickness, Type 3 eyes displayed a much greater decrease than Type 1. The greater baseline retinal thickness is the result of more significant baseline IRF associated with Type 3 lesions. Type 3 lesions resolved more rapidly with anti-VEGF therapy during the early course, resulting in a smaller difference in thickness between the 2 lesion types at final follow-up.

The predominant exudative sign in Type 1 lesions is SRF likely as a result of disruption of the RPE pump mechanism. Type 3 lesions may also develop SRF, typically eccentric to the PED and its associated neovascular focus. The association rate, however, is low because the subretinal compartment is sealed off by the intraretinal neovascular complex as it grows into the RPE.[2] As a result, Type 1 lesions have a significantly greater initial SRF volume and consequently greater decrease over 12 months (vs. Type 3 lesions) as shown in our study.

Although our study showed a good functional and anatomical response to treatment, care must be taken when associating these two categories of outcomes. The PED size, SRF volume, mean central SRF thickness, and SRHRM volume all failed to predict BCVA at baseline and follow-up for Type 1 and Type 3 eyes with simple linear regression. Central retinal thickness was found to be predictive of final BCVA in Type 1 eyes without RPE tears, but was not predictive in Type 3 eyes or the overall Type 1 cohort. The presence of IRF in eyes with Type 1 NV may indicate a more chronic lesion with a worse prognosis because of associated disruption of the outer retina (including the external limiting membrane) and RPE. Additionally, the presence of SRF in eyes with Type 3 NV may indicate more adverse or chronic disease. In fact, at baseline, Type 1 eyes with IRF and Type 3 eyes with SRF were found to have worse vision than their counterparts without that type of fluid. At final 12-month follow-up, however, no Type 3 eyes had residual SRF and Type 1 eyes with IRF also had a lower average BCVA but with a large SD, this difference was not statistically significant. Interestingly, Type 1 eyes that began with IRF and Type 1 and Type 3 eyes that began with SRF seemed to maintain a worse BCVA at final 12-month follow-up; however, with the wide range of visual acuities and small sample size, these findings were not statistically significant in our study.

In summary, care must always be taken to extrapolate anatomical success with functional success. This finding is consistent with multiple previous reports on AMD, diabetic retinopathy, and retinal vein occlusions that show correlations between anatomical outcome and visual results are variable.[22,23] Thus, this underscores the important point that although OCT-measured anatomical values may serve as useful tools to gauge clinical progress, they cannot substitute as surrogates for visual acuity measurements in the course of treatment.

Although Type 1 (excluding RPE tears) and Type 3 PEDs were noted to demonstrate similar dimensions (maximal height and volume) at baseline, Type 3 PEDs were smaller at final follow-up. In all PEDs, it seemed that the serous component was the first to decrease with injections. Additionally, 36% of Type 1 lesions had multilayering[12,24] at baseline that increased to 68% at final follow-up. In contrast, none of the Type 3 lesions ever developed this feature. Multilayering in fibrovascular PEDs has been described as a lamellar layering of homogenous hyperreflective bands with clefts.[12,24] This sub-RPE material is believed to be fibrocellular tissue that is sequentially deposited over time forming a scar. In these Type 1 lesions, as the serous component resolves, this scaffolding structure along with any residual fibrovascular material prevents the continued shrinkage of the PED. In contrast, Type 3 lesions originate above the RPE and cause a largely serous PED with minimal, if any, sub-RPE fibrovascular material. As the serous fluid resolves, there is minimal sub-RPE fibrovascular tissue, leading to a more complete flattening or resolution of the PED than Type 1 lesions.

A smaller number of injections was needed for the complete regression of SRF and IRF in eyes with Type 3 versus Type 1 NV. Additionally, fewer Type 3 eyes required pro re nata injections in the latter half of the study. Given the fewer number of injections needed to achieve and maintain fluid regression and the concern that excessive intravitreal anti-VEGF injections can expedite GA, Type 3 lesions may do better with a less aggressive treatment plan. Additionally, clinical trials studying different treatment regimens for neovascular AMD should account for possible differences in response between the subtypes of AMD when analyzing their results.

The population of Type 1 eyes that experienced RPE tears showed a much larger PED size at baseline (849 ± 256 μm for PED maximal height and 4.2 ± 2.5 mm^3 for PED volume) and worse visual outcomes at final follow-up. The final BCVA of these eyes varied significantly and depended on the location of the tear. If the RPE tears affected the fovea, vision was significantly jeopardized while a more eccentric tear supported good vision. In our study, all tears were either grade 3 or 4, explaining the poor visual outcome in this group. For eyes that appear high risk for RPE tears due to a large PED size (quoted as a height of 600 μm or greater)[25] and presence of SD-OCT signs of contraction with associated SRF, certain studies have proposed the use a lower dosage of anti-VEGF therapy to reduce contractile forces believed to be the causative factor of RPE tears[26–28] although this awaits further validation.

Our study has limitations. Although it was a prospective study, a priori power calculations were not performed to set a target sample size for enrollment and our final enrollment sample size was small especially for Type 3 lesions. As such, comparisons and correlation analysis that did not reach statistical significance may represent real effects without statistical significance because of a small sample size. However, given the dramatic differences in baseline morphology and treatment response between Type 1 and Type 3 lesions, many meaningful comparisons that were statistically significant were still found despite the small sample size. Additionally, our study was limited to a 1-year duration with a strict treatment regimen that may or may not be applicable to a real-world clinical practice. Although long-term clinical studies for AMD are important given the chronicity of the disease, we believed that this duration was adequate to emphasize the remarkable difference in functional and anatomical outcomes between Type 1 and Type 3 lesions, which was the primary goal. Longer-term studies would be needed to truly assess the visual comparisons as GA either secondary to the natural progression of AMD or expedited by intravitreal injections may play a greater role with time.

Studies investigating the efficacy of intravitreal aflibercept therapy of PEDs in AMD have mostly shown good anatomical response with improvement or no significant change in visual acuity. However, these investigations are limited in number, are retrospective in design, small in terms of sample sizes, or use time-domain OCT.[29–34] They also fail to differentiate between Type 1 and Type 3 NV. Our prospective study shows excellent functional and anatomical improvement of PEDs with aflibercept monotherapy. However, fundamental visual and anatomical differences exist between PEDs caused of Type 1 versus Type 3 NV at baseline and at follow-up that may affect diagnosis and therapy. As illustrated in our study, it is useful for the clinician to differentiate between the NV subtype at the time of diagnosis of the PED because the differences in response to treatment and the required number of injections may affect optimal management.

Key words: aflibercept, age-related macular degeneration, imaging, intravitreal injection, optical coherence tomography, pigment epithelial detachment, retinal angiomatous proliferation, type 1 neovascularization, type 3 neovascularization, vascular endothelial growth factor.

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